



Nanobots in Lung Cancer Therapy: An Overview

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ABSTRACT	Review Article
Lung cancer remains the leading cause of cancer related death worldwide. It is responsible for roughly 18.4% of all cancer deaths [1]. Late-stage diagnosis, drug resistance and the limitation of getting a therapeutic agent precisely to the lung tumor site continues to be major drawbacks. Nanoparticle based drug delivery has advantages toward solving this problem due to its tiny size, distribution and precise absorption in tumor site. Such tumor targeting improves bioavailability. ‘Nanorobots’ or ‘Nanobots’ are nanoscale devices function on autonomous or semi-autonomous principle and capable of navigating through biological environment to exhibit programmable drug release at the targeted site. This review provides a broad overview of the major classes of nanobots being explored for lung cancer therapy, namely <i>synthetic</i>, <i>biohybrid</i> and <i>DNA origami</i> systems. This piece of the article also attempts to discuss various routes used to administer these nanobots and the mechanisms through which they act on tumors. Their emerging roles in the diagnosis are also considered. Finally, the challenges, limitations and future perspectives were also considered under its purview. Keywords: Lung Cancer; Nanoparticles; Nanobots; Synthetic, Biohybrid, DNA Origami Systems; Theranostics.	Article History
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1. INTRODUCTION

Lung cancer is one of the most aggressive malignancies affecting the people worldwide. It is the disease’s mortality burden more than its incidence alone that keeps it at the center of oncology research [1]. Non-small cell lung cancer (NSCLC) accounts for roughly 85% of all cases while the remainders are mostly of small cell lung cancer (SCLC) type. Lung cancer often diagnosed at an advanced stage. By the time a tumor is found, it has already progressed or begun to develop resistance to standard therapies. Conventional chemotherapeutic agents happen to be in the systemic circulation and thereby expose healthy tissue to these toxic agents intended for the tumor. As a result, side effects are produced which can substantially reduce patient’s quality of life [2,3].

Nanotechnology has reshaped this picture over the past two decades by enabling drug delivery systems at nanoscale. Such approach can improve a drug’s bioavailability by encouraging its accumulation preferentially in tumor tissues followed by controlling its release over time. The newest development along this line of research is ‘Nanorobot’ or ‘nanobot’. A nanobot is designed to navigate actively in the bio-environment to locate the tumor i.e. the target site and deliver its cargo

in a programmed way. The size of most nanobots range from 1 to 200 nanometers which appears to be a huge advantage for these nanobots to travel through the fine vasculature and interact directly with individual tumor cells [1,4].

Physicist Richard Feynman is generally credited with first articulating the idea of machines built and operating at the molecular scale. That early vision underlies much of today’s nanorobotic research [1,4,5]. Today’s nanobots are capable of navigating in the biological environment in an automatic or semi-automatic manner and perform therapeutic functions like drug delivery, imaging and tumor ablation precisely. Three broad categories of nanobots have emerged and being experimented in lung cancer therapy. These are synthetic nanobots built from metals, polymers, hydrogels, silica or magnetic materials; biohybrid nanobots which combine living cells with synthetic components; and DNA origami nanobots which uses folded strands of DNA as a programmable scaffold for carrying a therapeutic payload [6,7]. Such various categories of nanobots are being explored for targeted drug delivery, controlled drug release, photothermal therapy and gene therapy [2,7,8]. They can be introduced into the body by inhalation, intravenous injection or

direct intratumoral injection [3,6,9]. Beyond therapy, functionalized nanobots are also being investigated as diagnostic tools. None of these are yet in routine clinical use, but the technology has successfully advanced from laboratory experiments into human clinical trials. Most of the applications are focused on oncology and their passive or active navigation can delivered their payload to the hard to reach tumors.

Manufacturing nanobots uniformly and reproducibly at industrial scale remains an engineering challenge [6]. The nanobot research should imbibe AI assisted design of nanobot structures, personalized lung cancer therapy approaches, CRISPR based gene editing payloads, more sophisticated biomimetic designs and multi functional theranostic platforms to diagnose and treat simultaneously [8]. Nanorobots or nanobots are largely different from ordinary nanoparticles. Nanoparticles carry a payload with them and by passive or stimuli responsive means navigate into the tumor. They improve bioavailability and reduce systemic toxicity however, they do not generate their own motion [5]. Nanobots combine the properties of nanoparticles property along with the functional ability to navigate, sense the local bioenvironment and interact with individual cells with such a precision that a passive carrier cannot match. Most nanorobots convert the external energy like magnetic, acoustic, chemical, or light into a mechanical motion empowering it to navigate through bio-environment. This character precisely separates them from ordinary nanoparticles. Another variant is *biohybrid nanorobot* which pairs synthetic materials with a biological component such as bacteria or a cell fragment. Such nanomaterials are capable to move naturally and able to release their payloads into the target site utilizing the property of tissue tropism [10]. This review attempts to provide an overview on the current status of nanobot research in the vicinity of lung cancer therapy.

2. CATEGORIES OF NANOBOTS USED IN LUNG CANCER TREATMENT

2.1 Synthetic Nanobots

Synthetic nanobots are synthesized from metals, polymers, hydrogels, silica and magnetic materials. Their movement in bio-environment is

typically governed from outside the body and in such cases the trigger may be an external magnetic field, ultrasound, or light. Their surfaces can be functionalized with tumor targeting ligands such as antibodies to locate the receptors over expressed on lung cancer cells such as *epidermal growth factor receptor* (EGFR) and *programmed death-ligand1* (PD-L1) [7]. This surface modification allows this nanostructure to seek out cancer cells specifically, rather than distributing indiscriminately throughout the body.

2.2 Biohybrid Nanobots

Biohybrid nanobots combine living cells with synthetic materials. Several working examples already exist in preclinical research like algae based microrobots; bacteria powered nanobots; and carriers derived from immune cells are among these. The appeal of this approach is that it uses natural biological mobility and tissue tropism to improve targeting efficiency and at the same time reduce immunogenicity. Tissue tropism is a tendency of viruses, nanoparticles or cellular vectors to preferentially target a tissue. Recently, algae based inhalable microrobots are introduced which have shown extended retention in lung tissue and even distribution of their drug payload throughout pulmonary structures. Because they are administered through inhalation, they are comparatively easy for patients to use [6].

2.3 DNA Origami Nanobots

DNA origami nanobots take a different engineering approach altogether. The method utilizes the natural base pairing rule of DNA where Adenine (A) binds to Thymine (T) and Guanine (G) to Cytosine (C) and thereby a long single stranded DNA folds into a 'scaffold' structure where hundreds of shorter strands known as 'staple' strand helps to fix the architecture. This programmable folded structure of DNA is capable of carrying therapeutic payload. Such nanobots stay inactive until they encounter a specific tumor biomarker. In presence of the appropriate biomarker, they undergo a structural change to release their payload directly within the tumor microenvironment. In one well studied example, enzyme thrombin was loaded into DNA nanobot. The nanobot triggered localized clotting in tumor blood vessels and produce measurable tumor regression in that preclinical lung cancer model [6].

Table 1 Examples of nanobots from different category along with the research groups associated with their development.

Type of Nanobot	Example	Developing Institution / Reference
Magnetic nanobots	Magnetically driven helical nanorobot	ETH Zurich and collaborators [11]
Biohybrid nanobots	Magnetically driven helical nanorobot	Leibniz Institute for Solid State and Materials Research [12]
DNA Origami nanobots	DNA nanorobot for targeted cancer therapy	Arizona State University and National Center for Nanoscience and Technology [13]
Surgical nanobots	Microgripper nanorobot	Johns Hopkins University [14]
Enzyme powered nanomotors	Urease/catalase nanomotors	Institute for Bioengineering of Catalonia (IBEC), Spain [15]

3. ROUTES OF NANOBOT ADMINISTRATION

3.1 Inhalation Delivery

Inhalation is the most natural route for treating lung cancer. Therefore, it remains one of the most actively explored delivery routes for nanobots in such patients. Inhaled nanobots bypass first-pass metabolism and deposits directly onto the pulmonary tissues. This translates into high local drug concentrations without systemic exposure that intravenous administration involves. Recent work on inhalable *biohybrid microbots* has reported even distribution throughout lung tissue and retention times exceeding five days in animal models [3].

3.2 Intravenous Administration

Introducing nanobots into the bloodstream through intravenous route allows them to accumulate in lung tumors through a combination of active and passive targeting mechanisms. Both DNA nanobots and magnetically guided nanobots have produced encouraging results in targeting pulmonary tumors following systemic administration [9].

3.3 Intratumoral Injection

Injecting nanobots directly into a tumor sidesteps much of the targeting problem altogether. This allows highest possible local drug concentration while limiting systemic exposure. This approach is invasive and useful for accessible tumors or during surgical interventions [6].

4. NANOBOT'S IN LUNG CANCER: THE WAY THEY WORK

4.1 Targeted Drug Delivery

The core purpose of *nanobot* is to get the drug into the tumor. Such tumor specific targeting can occur through several mechanisms as presented below:

i) Passive targeting via EPR effect: Rapidly growing solid tumors need a lot of food and oxygen. So, the body grows lots new blood vessels. These newly formed blood vessels are defective and leaky. They have large gaps between their endothelial cells. Due to this leaky abnormal vasculature, the permeability of nano materials into the tumor enhances. Further, tumors lack proper lymphatic drainage system for which the fluids and waste are not drained out of the tumor properly. This allows the nanoparticles or nanobots which entered into the tumor tissue passively through the leaky blood vessels become trapped and build over time utilizing this *Enhanced Permeability and Retention* (EPR) effect.

ii) Active targeting: Surface bound antibodies or ligands assist the nanobots to locate and bind specifically to lung cancer cells actively. This process bypasses healthy tissues.

iii) Magnetic guidance: An externally applied magnetic field can steer drug loaded nanobots through the bloodstream or bronchial passages directly toward the lung tumor.

iv) Acoustic guidance: Non invasive sound waves can similarly guide, track and trigger nanobots deep within the lung tissue.

Together, these approaches elevates drug concentration at the tumor site while limiting the systemic toxicity associated with conventional chemotherapy [2,7].

4.2 Stimuli Responsive Drug Delivery

Once a nanobot reaches its target, it needs to know when to release the payload. To perform this seamlessly, several trigger mechanisms have been developed which are as follows:

i) pH sensitivity: Because tumor tissue tends to be more acidic than healthy tissue, nanobots can be engineered to release their payloads only under acidic conditions. In other environmental pH condition, they shall remain inert.

ii) Enzymatic triggers: Tumors are often enzyme rich in comparison to the surrounding tissues. This local enzymatic activity can serve as a marker that a nanobot uses both to recognize the tumor site and to release its payload.

iii) Thermal triggers: Some nanobots are designed in a way to generate precise, localized rise in temperature sufficient to destroy cancer cells while sparing surrounding healthy lung tissue.

iv) Magnetic triggers: A magnetic field can first guide a nanobot to the tumor site and then can trigger to release the cargo in a targeted manner.

v) Light based triggers: A specific wavelength of external light can act as stimuli to target nanobot to the lung tumor site.

The combined effect of these stimuli responsive strategies are capable to concentrate the therapeutic effect within the tumor while reducing collateral damage to the healthy tissue [7,8].

4.3 Photothermal Therapy and Gene Therapy

Photothermal nanobots work by absorbing near infrared (NIR) light and converting it into localized heat capable of destroying lung cancer cells. Combined chemo-photothermal approaches using nanotechnology have already been demonstrated in lung cancer models [6]. Gene therapy nanobots, used to ferry therapeutic nucleic acids like DNA, mRNA, siRNA, and CRISPR-Cas9 components directly into the tumor cells. Such delivery aims to silence oncogenes, restore the function of tumor suppressor genes or sensitize tumors to be more responsive towards chemotherapy and immunotherapy [6].

5. NANOBOTS IN THE DIAGNOSIS OF LUNG CANCER

Nanobots' usefulness is not confined only to treatment but to the early diagnosis. Functionalized nanobots can detect tumor biomarkers, track disease progression and enhance the sensitivity of existing imaging modalities such as MRI, CT, PET and fluorescence. Because they can identify cancer cells at very low concentrations, they hold promise for early stage detection. This early detection is one of the biggest advantage for improving lung cancer outcomes [8,16]. Theranostic nanobots take this a step further by combining diagnostic and therapeutic functions in a single platform, allowing simultaneous imaging and monitoring of patient's response to the treatment in real time [7,16].

6. RECENT ADVANCES IN NANOBOT BASED LUNG CANCER THERAPY

Several of the developments described above have already moved from the level of concept to the demonstrated preclinical result. Biohybrid systems that carry drug loaded nanoparticles are capable of self propulsion within pulmonary tissue. They have shown improved survival in animal models with lung metastasis [6]. DNA origami nanobots carrying thrombin have successfully induced localized tumor vessel thrombosis and inhibited tumor growth in similar models [6]. Advanced nanocarriers engineered to respond to tumor specific conditions like acidic pH, elevated enzymatic activity or other tumor micro-environmental stimuli for precise drug release [7]. Exosome inspired delivery systems have demonstrated favorable biocompatibility, prolonged circulation and strong tumor targeting behavior [7].

7. CHALLENGES AND LIMITATIONS

Nanobot based lung cancer therapy till date remains in the research stage and substantial challenges persist. One important aspect of nanobots is its reproducibility and safety in every single batch. This requirement must match with the expectations of the regulators to win the trust of the clinicians [6]. Beside production, few more challenges persist which warrants serious investigation. These issues include their potentiality to cause toxicity, how the body react to their long term accumulation in the body, how the immune system responds to them, and how or whether they biodegrade safely etc. need to be investigated [4,10].

The regulatory frameworks of today are not fully equipped to evaluate nanobot systems. The existing frameworks are largely built around conventional pharmaceuticals and simpler nanoparticulate systems. Therefore, new standards need to be developed to assess the safety, efficacy and manufacturing quality of nanobot systems [16]. Once a nanobot is inside a patient's body, it is technically difficult to monitor it. To do this work responsibly, we need to have advanced reliable imaging and navigation technology [6]. If we consider these

challenges and really eager to turn these nanobots from laboratory scale to an affordable, mass producible clinical option, then considerable work must be undertaken.

8. CONCLUSION AND FUTURE PERSPECTIVES

In future, the nanobot research should incorporate the AI assisted design of nanobot structures, personalized lung cancer therapy approaches, CRISPR based gene editing payloads, more sophisticated biomimetic designs and multi functional theranostic platforms that diagnose and treat simultaneously [8]. If artificial intelligence, synthetic biology, nanotechnology and precision medicine continue to converge, then the evolved intelligent nanobots could plausibly reach the point of diagnosing, treating and monitoring lung cancer [8]. However, the pace of progress in this field suggests the possibility of nanobots clinical application. More clinical trials involving nanobots could potentially explain its functioning inside the human body [6]. Some early results show that the nanobots are capable of detecting 12 cancer cells at a time [7].

This review has intentionally stayed at the level of theory and concept rather than original experimental work. We began with an overview of nanobots construction and mechanisms of action as they apply specifically to lung cancer treatment [1-10,16]. As a whole, it appears that nanobots are likely to become a meaningful part of drug delivery and diagnostic landscape for lung cancer therapy.

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